Dosimetry in clinical radionuclide therapy: the devil is in the detail…

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Radionuclide therapy (RNT), also known as “targeted”, “metabolic” or “molecular” radiotherapy uses open (i.e. “unsealed”) radioactive isotopes, generally administered orally or intravenously, enabling the delivery of a high radiation dose to the target, while minimising normal-tissue toxicity. This systemic form of radiation therapy has distinct similarities, but also profound differences as compared to the more commonly used external beam radiotherapy (EBRT). From another perspective, RNT can be better characterised as a tumour-selective treatment modality with more similarities to systemic chemotherapy [1].

The amount of transferred energy in joules per unit mass (Kg) of target tissue is expressed in grays (Gy); 1 Gy = 1J/Kg. This absorbed radiation dose unit is also employed in EBRT.Actually, the term “radiation dose” covers three kinds of dose: “absorbed dose” expressed in mGy indicating the amount of energy deposited by radiation in a mass, “equivalent dose” (absorbed Dose x the appropriate radiation weighting factor in function of the type of

radiation; e.g. α,β, χ or neutrons) expressed in mSv to an organ and "effective dose" (sum of equivalent doses to all organs, each adjusted with the appropriate tissue weighting factor; taking in account the sensitivity of the organ to radiation) expressed in mSv for the whole body. The 3 kinds of radiation dose should not be confounded with the frequently used term, in the context of radionuclide therapy, "activity dose" that refers to the administered activity expressed in MBq.

While CT can be used for relatively straightforward calculation of the absorbed dose in EBRT, in RNT the spatial and temporal distribution of radiation, within the time interval of the decaying isotope, is extremely complex, depending on a highly dynamic interplay of pharmacokinetics aspects (such as perfusion, metabolism, target expression heterogeneity, transmembrane cellular uptake, intracellular degradation, radionuclide release, and excretion), repair mechanisms and radiobiological phenomena (low and continuously decreasing dose rate).

In order to estimate the local absorbed dose, integral activities rely on accurate detection of the activity distribution over time. However, due to the limited spatial resolution of imaging devices, calculations are based on approximation and it is important to note that it is not possible to perform the "perfect" dosimetry study. To date, the need for and added value of dosimetry to optimise the therapeutic activity dose for the individual patient has been far from self-evident. RNT dosimetry has not gained wide acceptance as a clinical tool in the nuclear medicine community because of an imbalance between the lack of accuracy and the complexity of time-consuming and costly procedures, potentially posing a significant burden to our patients and our health care systems. Moreover, the necessary specialised knowledge and experience required to perform accurate dosimetry studies is not available in all clinical centres, therefore potentially limiting the offer to patients. A number of clinical studies have completely refrained from dosimetry, instead using fixed activities for all patients or individualised activity doses based on body weight or body surface area. Indeed, after seven decades of treating thyroid cancer patients, international guidelines still do not provide an unequivocal recommendation on the amount of radioiodine that should be given [1].

For those reasons, rather than seeking similarities to EBRT, it is more appropriate to develop RNT similar to chemotherapeutics, where dose calculation based on body weight or body surface area is common practice, independent of the tumour load and metastases. The maximal tolerated dose of chemotherapeutics is established during clinical studies. In

subsequent clinical practice, the level of chemotherapeutic in blood is not checked to investigate the biodistribution and the delivery to the tumours.

Official guidelines and recommendations for-RNT do not include advanced dosimetric calculations. Like in the chemotherapy, fixed radioactivity doses (with or without visual assessment of pretherapy scans) or body weight or body surface area based activity doses are considered sufficient in clinical practice for the main clinical RNT protocols. Nevertheless, the European Council Directive 2013/59 [2], to be translated into national legislations before 6 February 2018, stipulates that in medical exposures for radiotherapeutic purposes, including RNT, exposures of target volumes shall be individually planned and their delivery appropriately verified.

In a recent article published in this Journal, Chiesa et al. [3] pointed out this aspect. While these authors recognize that in RNT “the absorbed dose to the target volume cannot be calculated or reliably predicted for technical or practical reasons”, a solution “to base therapy planning on the maximum tolerable absorbed dose (MTAD) to nontarget organs or tissues” is advocated. The authors do not explain why the nontarget solution is more feasible than target calculations, since the dosimetric procedures appear similar, hampered by the same errors of measurement (except for the evaluation of the irradiated volume) and by identical logistical issues. As these authors pointed out, dosimetry in disseminated disease is difficult and in many cases not possible. In RNT, maximal absorbed dose to tumours or metastases is required, but the activity dose is restricted by the absorbed dose to critical normal organs (e.g. kidney and bone marrow in peptide radionuclide therapy) to avoid irreversible deterministic effects. Furthermore, the strategy to individually calculate the maximum tolerated dose for normal organs with the goal to enhance therapeutic efficacy assumes that 1. the dose will increase in a therapeutically relevant manner in all lesions and 2. that the dose always predicts the outcome. Both assumptions ignore biology. The local dose depends not only on the administered activity but also on the expression of the target in tumor lesions which often show a high intralesional as well as interlesional heterogeneity. As stated above the efficacy of RNT is determined by pharmacokinetics and repair mechanisms. Since RNT is often applied in patients at later stages and after various treatments we face tumors with increased heterogeneity and optimized escape strategies. In our opinion, dosimetry should be a quantitative procedure that unequivocally provides additional clinical benefit over standard procedures to the individual patients. Dosimetry

should play an important role when a new agent for RNT undergoes clinical testing, alongside assessment of the maximum tolerated dose and of side-effects, similar to clinical trials of non-radioactive oncological drugs. In the clinical setting, the statement of DeNardo et al. [4] postulated more than 15 years ago is still valid: “claims for specific dosimetry have to demonstrate that the frequency of excess toxicity and/or tumour underdosing significantly decreases”. From a clinical point of view, dosimetry studies could be considered in current daily clinical practice when treating patients with risk factors [5].
Another important factor is represented by radiobiological effects of RNT at the cellular and molecular level [6]. Extrapolations made from EBRT are wrong, due to the fundamental differences in dose rate and mechanisms of inflicting damage to the DNA. In RNT, with its decreasing dose rate, tumour DNA repair takes place simultaneously with sublethal damage [7]. Furthermore, it was recently reported that sensitivity to low-absorbed dose, low-dose rate radiation displays a genetically-induced individual variability. [8, 9].

In conclusion, although dosimetry is an undisputed aspect of radiopharmaceutical development, its clinical use to tailor the administered activity to an individual patient’s needs is less evident. Data in the literature clearly and unequivocally establishing the potential of dosimetry to avoid under- and overdosing and to standardise radionuclide therapy methods are very scarce. Furthermore, dosimetry is a difficult procedure that is not available everywhere as specialised knowledge and experience are required. Thus, we must be cautious before transferring complex dosimetry to routine clinical practice, while robust scientific justification remains to be established. First and foremost, the nuclear medicine community at large has the obligation to prove in prospective and randomised trials with adequate methodology, that complex dosimetry-based radionuclide therapy has clinically relevant additional benefits for our patients over the currently used, well-established and very safe empiric dosing methods, whether using fixed-activity concepts or based on simple characteristics such as body weight and body surface area.

Compliance with Ethical Standards:

* Disclosure of potential conflicts of interest: Authors declare NO conflict of interest in this field

* Research involving human participants and/or animals: NO research article

* Informed consent: NO informed consent needed

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